NDA 20-628/SLR-014

Hoffman-La Roche, Inc
Afln: Barbara S. Taylor, PhD
Program Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley,NJ 07110-1199

Dear Dr. Taylor:

Please refer to your supplemental new drug application (SLR-014) dated and received December 23, 1999 submitted under section 505(b) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for INVIRASE® (saquinavir MESYLATE) 200 mg Capsules.

We acknowledge receipt of your submissions dated March 6, 2000, May 4, 2000, August 8, 2000, and September 26, 2000.

This "Changes Being Effected" supplemental new drug application (SLR-014) provides for the following updated safety information:

(1) Drug interactions with the statins and sildenafil (VIAGRA);
(2) Information on fat redistribution;
(3) Information on pregnancy and breastfeeding;
(4) Information on geriatric use; and
(5) Information on the differentiation between FORTOVASE and INVIRASE.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed-upon labeling text. Accordingly, this application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) dated September 26, 2000.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please mount individually ten of the copies on heavyweight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-628/SLR-014." Approval of this submission is not required before the labeling is used.

If a letter communicating important information about this drug product, (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy of the following address:

MED WATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager at (301) 827-2335.

Sincerely,

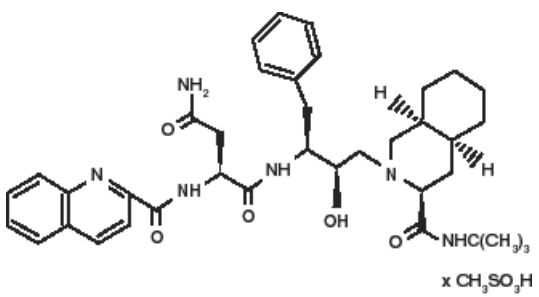
Heidi M. Jolson, MD, MPH
Director
Division of Antiviral Drug Products
Center for Drug Evaluation and Research

INVIRASE®
(saquinavir mesylate)
CAPSULES

WARNING:

INVIRASE® (saquinavir mesylate) capsules and FORTOVASE® (saquinavir) soft gelatin capsules are not bioequivalent and cannot be used interchangeably. When using saquinavir as part of an antiviral regimen FORTOVASE is the recommended formulation. In rare circumstances, INVIRASE may be considered if it is to be combined with antiretrovirals that significantly inhibit saquinavir's metabolism (see CLINICAL PHARMACOLOGY: *DRUG INTERACTIONS*).

DESCRIPTION: INVIRASE brand of saquinavir mesylate is an inhibitor of the human immunodeficiency virus (HIV) protease. INVIRASE is available as light brown and green, opaque hard gelatin capsules for oral administration in a 200-mg strength (as saquinavir free base). Each capsule also contains the inactive ingredients lactose, microcrystalline cellulose, povidone K30, sodium starch glycolate, talc and magnesium stearate. Each capsule shell contains gelatin and water with the following dye systems: red iron oxide, yellow iron oxide, black iron oxide, FD&C Blue #2 and titanium dioxide. The chemical name for saquinavir mesylate is N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline- 3(S)-carboxamide methanesulfonate with a molecular formula $C_{38}H_{50}N_6O_5$ CH_4O_3S and a molecular weight of 766.96. The molecular weight of the free base is 670.86. Saquinavir mesylate has the following structural formula:



Saquinavir mesylate is a white to off-white, very fine powder with an aqueous solubility of 2.22 mg/mL at 25°C.

CLINICAL PHARMACOLOGY: ***Mechanism of Action:*** HIV protease cleaves viral polyprotein precursors to generate functional proteins in HIV-infected cells. The cleavage of viral polyprotein precursors is essential for maturation of infectious virus. Saquinavir mesylate, henceforth referred to as saquinavir, is a synthetic peptide-like substrate analogue that inhibits the activity of HIV protease and prevents the cleavage of viral polyproteins.

Microbiology: *Antiviral Activity In Vitro:* The in vitro antiviral activity of saquinavir was assessed in lymphoblastoid and monocytic cell lines and in peripheral blood lymphocytes. Saquinavir inhibited HIV activity in both acutely and chronically infected cells. IC50 values (50% inhibitory concentration) were in the range of 1 to 30 nM. In cell culture saquinavir demonstrated additive to synergistic effects against HIV in double- and triple-combination regimens with reverse transcriptase inhibitors zidovudine (ZDV), zalcitabine (ddC) and didanosine (ddI), without enhanced cytotoxicity.

Resistance: HIV isolates with reduced susceptibility to saquinavir have been selected in vitro. Genotypic analyses of these isolates showed substitution mutations in the HIV protease at amino acid positions 48 (Glycine to Valine) and 90 (Leucine to Methionine).

Phenotypic and genotypic changes in HIV isolates from patients treated with saquinavir were also monitored in Phase 1/2 clinical trials. Phenotypic changes were defined as a 10-fold decrease in sensitivity from baseline. Two viral protease mutations (L90M and/or G48V, the former predominating) were found in virus from treated, but not untreated, patients. The incidence across studies of phenotypic and genotypic changes in the subsets of patients studied for a period of 16 to 74 weeks (median observation time approximately 1 year) is shown in Table 1. However, the clinical relevance of phenotypic and genotypic changes associated with saquinavir therapy has not been established.

Table 1. Frequency of Genotypic and Phenotypic Changes in Selected Patients Treated With Saquinavir

	Genotypic*		Phenotypic#	
	24 Week	1 Year	24 Week	1 Year
Monotherapy	3/8 (38%)	15/33 (45%)	2/22 (9%)	5/11 (45%)
Combination Therapy	5/30 (17%)	16/52 (31%)	0/23 (0%)	11/29 (38%)

*Double mutation (G48V and L90M) has occurred in 2 of 33 patients receiving monotherapy. The double mutation has not occurred with combination therapy.

Phenotypic changes have been defined as at least a 10-fold change in sensitivity relative to baseline. In a few patients genotypic and phenotypic changes were unrelated.

Cross-resistance to Other Antiretrovirals: The potential for HIV cross-resistance between protease inhibitors has not been fully explored. Therefore, it is unknown what effect saquinavir therapy will have on the activity of subsequent protease inhibitors. Cross-resistance between saquinavir and reverse transcriptase inhibitors is unlikely because of the different enzyme targets involved. ZDV-resistant HIV isolates have been shown to be sensitive to saquinavir in vitro.

Pharmacokinetics: The pharmacokinetic properties of saquinavir have been evaluated in healthy volunteers (n=351) and HIV-infected patients (n=270) after single- and multiple-oral doses of 25, 75, 200 and 600 mg tid and in healthy volunteers after intravenous doses of 6, 12, 36 or 72 mg (n=21).

ABSORPTION AND BIOAVAILABILITY IN ADULTS: Following multiple dosing (600 mg tid) in HIV-infected patients (n=30), the steady-state area under the plasma concentration versus time curve (AUC) was 2.5 times (95% CI 1.6 to 3.8) higher than that observed after a single dose. HIV-infected patients administered saquinavir 600 mg tid, with the instructions to take saquinavir after a meal or substantial snack, had AUC and maximum plasma concentration (C_{max}) values which were about twice those observed in healthy volunteers receiving the same treatment regimen (Table 2).

Table 2. Mean (%CV) AUC and C_{max} in Patients and Healthy Volunteers

	AUC_{8}(dose interval) (ng h/mL)	C_{max} (ng/mL)
Healthy Volunteers (n=6)	359.0 (46)	90.39 (49)
Patients (n=113)	757.2 (84)	253.3 (99)

Absolute bioavailability averaged 4% (CV 73%, range: 1% to 9%) in 8 healthy volunteers who received a single 600-mg dose (3 x 200 mg) of saquinavir following a high fat breakfast (48 g protein, 60 g carbohydrate, 57 g fat; 1006 kcal). The low bioavailability is thought to be due to a combination of incomplete absorption and extensive first-pass metabolism.

FOOD EFFECT: The mean 24-hour AUC after a single 600-mg oral dose (6 x 100 mg) in healthy volunteers (n=6) was increased from 24 ng h/mL (CV 33%), under fasting conditions, to 161 ng h/mL (CV 35%) when saquinavir was given following a high fat breakfast (48 g protein, 60 g carbohydrate, 57 g fat; 1006 kcal). Saquinavir 24-hour AUC and C_{max} (n=6) following the administration of a higher calorie meal (943 kcal, 54 g fat) were on average two times higher than after a lower calorie, lower fat meal (355 kcal, 8 g fat). The effect of food has been shown to persist for up to 2 hours.

DISTRIBUTION IN ADULTS: The mean steady-state volume of distribution following intravenous administration of a 12-mg dose of saquinavir (n=8) was 700 L (CV 39%), suggesting saquinavir partitions into tissues. Saquinavir was approximately 98% bound to plasma proteins over a concentration range of 15 to 700 ng/mL. In 2 patients receiving saquinavir 600 mg tid, cerebrospinal fluid concentrations were negligible when compared to concentrations from matching plasma samples.

METABOLISM AND ELIMINATION IN ADULTS: In vitro studies using human liver microsomes have shown that the metabolism of saquinavir is cytochrome P450 mediated with the specific isoenzyme, CYP3A4, responsible for more than 90% of the hepatic metabolism. Based on in vitro studies, saquinavir is rapidly metabolized to a range of mono- and di-hydroxylated inactive compounds. In a mass balance study using 600 mg ^{14}C-saquinavir (n=8), 88% and 1% of the orally administered radioactivity was recovered in feces and urine, respectively, within 5 days of dosing. In an additional 4 subjects administered 10.5 mg ^{14}C-saquinavir intravenously, 81% and 3% of the intravenously administered radioactivity was recovered in feces and urine, respectively, within 5 days of dosing. In mass balance studies, 13% of circulating radioactivity in plasma was attributed to unchanged drug after oral administration and the remainder attributed to saquinavir metabolites. Following intravenous administration, 66% of circulating radioactivity was attributed to unchanged drug and the remainder attributed to saquinavir metabolites, suggesting that saquinavir undergoes extensive first-pass metabolism.

Systemic clearance of saquinavir was rapid, 1.14 L/h/kg (CV 12%) after intravenous doses of 6, 36 and 72 mg. The mean residence time of saquinavir was 7 hours (n=8).

SPECIAL POPULATIONS: Hepatic or Renal Impairment: Saquinavir pharmacokinetics in patients with hepatic or renal insufficiency has not been investigated (see PRECAUTIONS).

Gender, Race and Age: Pharmacokinetic data were available for 17 women in the Phase 1/2 studies. Pooled data did not reveal an apparent effect of gender on the pharmacokinetics of saquinavir.

The effect of race on the pharmacokinetics of saquinavir has not been evaluated, due to the small numbers of minorities for whom pharmacokinetic data were available.

Saquinavir pharmacokinetics has not been investigated in patients >65 years of age or in pediatric patients (<16 years).

DRUG INTERACTIONS: HIVID and ZDV: Concomitant use of INVIRASE with HIVID® (zalcitabine, ddC) and ZDV has been studied (as triple combination) in adults.

Pharmacokinetic data suggest that the absorption, metabolism and elimination of each of these drugs are unchanged when they are used together.

Nelfinavir: In 14 HIV-positive patients, coadministration of nelfinavir (750 mg) with saquinavir [given as FORTOVASE (saquinavir), 1200 mg] resulted in an 18% (95% CI 5% to 33%) increase in nelfinavir plasma AUC and a 392% (95% CI 271% to 553%) increase in saquinavir plasma AUC (see PRECAUTIONS: *Drug Interactions*).

Ritonavir: Following approximately 4 weeks of a combination regimen of saquinavir (400 or 600 mg bid) and ritonavir (400 or 600 mg bid) in HIV-positive patients, saquinavir AUC and C_{max} values increased at least 17-fold (95% CI 9- to 31-fold) and 14-fold, respectively (see PRECAUTIONS: *Drug Interactions*).

Delavirdine: In 13 healthy volunteers, coadministration of saquinavir (600 mg tid) with delavirdine (400 mg tid) resulted in a 5-fold increase in saquinavir AUC. In 7 healthy volunteers, coadministration of saquinavir (600 mg tid) with delavirdine (400 mg tid) resulted in a 15% ± 16% decrease in delavirdine AUC (see PRECAUTIONS: *Drug Interactions*).

Nevirapine: In 23 HIV-positive patients, coadministration of saquinavir (600 mg tid) with nevirapine (200 mg bid) resulted in a 24% (95% CI 1% to 42%) and 28% (95% CI 1% to 47%) decrease in saquinavir plasma AUC and C_{max}, respectively (see PRECAUTIONS: *Drug Interactions*).

Ketoconazole: Concomitant administration of ketoconazole (200 mg qd) and saquinavir (600 mg tid) to 12 healthy volunteers resulted in steady-state saquinavir AUC and C_{max} values which were three times those seen with saquinavir alone. No dose adjustment is required when the two drugs are coadministered at the doses studied. Ketoconazole pharmacokinetics was unaffected by coadministration with saquinavir.

Rifampin: Coadministration of rifampin (600 mg qd) and saquinavir (600 mg tid) to 12 healthy volunteers decreased the steady-state AUC and C_{max} of saquinavir by approximately 80%.

Rifabutin: Preliminary data from 12 HIV-infected patients indicate that the steady-state AUC of saquinavir (600 mg tid) was decreased by 40% when saquinavir was coadministered with rifabutin (300 mg qd).

INDICATIONS AND USAGE: INVIRASE in combination with other antiretroviral agents is indicated for the treatment of HIV infection. This indication is based on results from studies of surrogate marker responses and from a clinical study that showed a reduction in both mortality and AIDS-defining clinical events for patients who received INVIRASE in combination with HIVID compared to patients who received either HIVID or INVIRASE alone.

Description of Clinical Studies: *Patients With Advanced HIV Infection and Prior ZDV Therapy:* Study NV14256 (North America) was a randomized, double-blind study comparing the combination of INVIRASE 600 mg tid + HIVID to HIVID monotherapy and INVIRASE monotherapy. The study accrued 970 patients, with median baseline CD_4 cell count at study entry of 170 cells/mm^3. Median duration of prior ZDV treatment was 17 months. Median duration of follow-up was 17 months. There were 88 first AIDS-defining events or deaths in the HIVID monotherapy group, 84 in the INVIRASE monotherapy group and 51 in the combination group. For survival there were 30 deaths in the HIVID group, 40 in the INVIRASE group and 11 deaths in the combination group.

The analysis of clinical endpoints from this study showed that the 18-month cumulative incidence of clinical disease progression to AIDS-defining event or death was 17.7% for patients randomized to INVIRASE + HIVID compared to 30.7% for patients randomized to HIVID monotherapy and 28.3% for patients randomized to INVIRASE monotherapy. The reduction in the number of clinical events for the combination regimen relative to both monotherapy regimens was statistically significant (see Figure 1 for Kaplan-Meier estimates of time to disease progression).

The 18-month cumulative mortality was 4% for patients randomized to INVIRASE + HIVID, 8.9% for patients randomized to HIVID monotherapy and 12.6% for patients randomized to INVIRASE monotherapy. The reduction in the number of deaths for the combination regimen relative to both monotherapy regimens was statistically significant (see Figure 2 for Kaplan-Meier estimates of time to death).

Figure 5 shows mean CD_4 changes over 48 weeks for the three treatment arms in study NV14256. Table 3 displays log RNA reductions at 16, 24 and 48 weeks among INVIRASE combination treatment arms in three clinical trials, including NV14256. Monotherapy arms are included for reference.

In ACTG229/NV14255, 295 patients (mean baseline CD_4=165) with prolonged ZDV treatment (median 713 days) were randomized to receive either INVIRASE 600 mg tid + HIVID + ZDV (triple combination), INVIRASE 600 mg tid + ZDV or HIVID + ZDV. In analyses of average CD_4 changes over 24 weeks, the triple combination produced greater increases in CD_4 cell counts (see Figure 4) compared to that of HIVID + ZDV. There were no significant differences in CD_4 changes among patients receiving INVIRASE + ZDV and HIVID + ZDV.

Comparisons of data across studies (NV14256 compared to ACTG229/NV14255) suggest that when INVIRASE was added to a regimen of prolonged prior zidovudine, there was little activity contributed by continuing ZDV.

Advanced Patients Without Prior ZDV Therapy: A dose-ranging study (Italy, V13330) conducted in 92 ZDV-naive patients (mean baseline CD_4=179) studied INVIRASE at doses of 75 mg, 200 mg and 600 mg tid in combination with ZDV 200 mg tid compared to INVIRASE 600 mg tid alone and ZDV alone.

In analyses of average CD_4 changes over 16 weeks, treatment with the combination of INVIRASE 600 mg tid + ZDV produced greater CD_4 cell increases than ZDV monotherapy (see Figure 3). The CD_4 changes of ZDV in combination with doses of INVIRASE lower than 600 mg tid were no greater than that of ZDV alone.

CONTRAINDICATIONS: INVIRASE is contraindicated in patients with clinically significant hypersensitivity to saquinavir or to any of the components contained in the capsule.

INVIRASE should not be administered concurrently with terfenadine, cisapride, astemizole, triazolam, midazolam or ergot derivatives. Inhibition of CYP3A4 by saquinavir could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions.

WARNINGS: New onset diabetes mellitus, exacerbation of preexisting diabetes mellitus and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

Concomitant use of INVIRASE with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including INVIRASE, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (eg, atorvastatin, or cerivastatin). Since increased concentrations of statins can, in rare cases, cause severe adverse events such as myopathy including rhabdomyolysis, this risk may be increased when HIV protease inhibitors, including saquinavir, are used in combination with these drugs.

PRECAUTIONS: ***General:*** INVIRASE (saquinavir mesylate) capsules and FORTOVASE (saquinavir) soft gelatin capsules are not bioequivalent and cannot be used interchangeably. Only FORTOVASE should be used for the initiation of saquinavir therapy (see DOSAGE AND ADMINISTRATION) since FORTOVASE soft gelatin capsules provide greater bioavailability and efficacy than INVIRASE capsules. For patients taking INVIRASE capsules with a viral load below the limit of quantification, a switch to FORTOVASE is recommended to maintain a virologic response. For patients taking INVIRASE capsules who have not had an adequate response or are failing therapy, if saquinavir resistance is clinically suspected, then FORTOVASE should not be used. If resistance to saquinavir is not clinically suspected, a switch to FORTOVASE may be considered.

The safety profile of INVIRASE in pediatric patients younger than 16 years has not been established.

If a serious or severe toxicity occurs during treatment with INVIRASE, INVIRASE should be interrupted until the etiology of the event is identified or the toxicity resolves. At that time, resumption of treatment with full-dose INVIRASE may be considered. For nucleoside analogues used in combination with INVIRASE, physicians should refer to the complete product information for these drugs for dose adjustment recommendations and for information regarding drug-associated adverse reactions.

Fig. 1.
Time to First AIDS-Defining Event (or Death) (days) NV14256

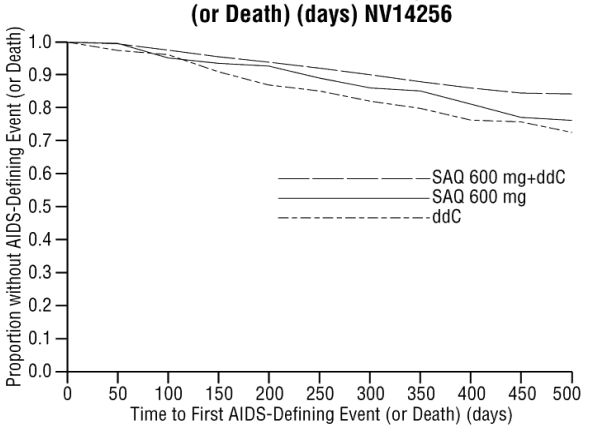


Fig. 2.
Time to Death (days) NV14256

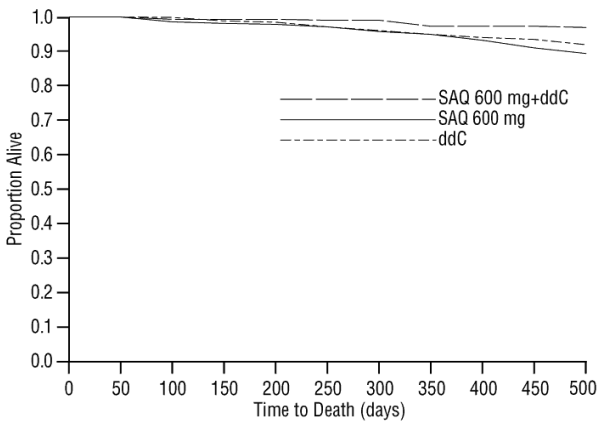
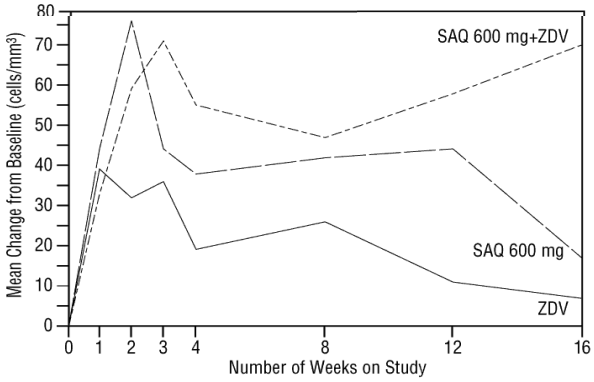
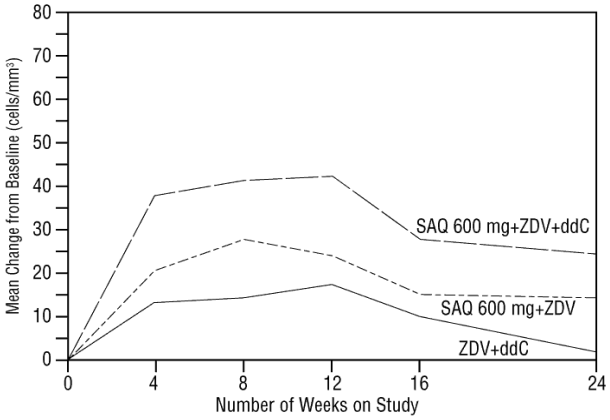


Fig. 3.
Mean CD_4 Changes (cells/mm^3) from Baseline in Study V13330 (Italy)



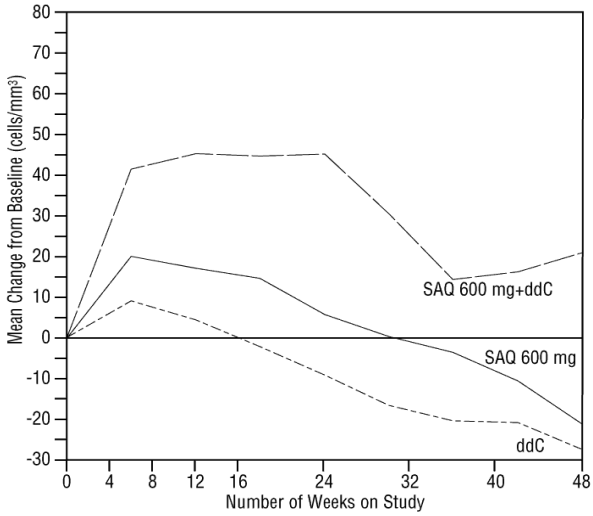
Number of Patients		
Week	0	16
SAQ	15	14
ZDV	13	12
SAQ+ZDV	15	14

Fig. 4.
Mean CD_4 Changes (cells/mm^3) from Baseline in Study ACTG229/NV14255



Number of Patients			
Week	0	12	24
ZDV+ddC	100	88	87
SAQ+ZDV	98	88	87
SAQ+ZDV+ddC	97	87	89

Fig. 5.
Mean CD_4 Changes (cells/mm^3) from Baseline in Study NV14256



Number of Patients				
Week	0	12	24	45
ddC	313	258	235	154
SAQ+ddC	307	271	255	179
SAQ	317	263	242	175

Table 3. Summary of Mean Log_{10} Plasma RNA Results from Major INVIRASE Clinical Studies

	V13330 (Italy) Naive patients			NV14255/ACTG229 (USA) ZDV-experienced			NV14256 (North America) ZDV-experienced		
	ZDV	SAQ*	ZDV+SAQ	ZDV+ddC	ZDV+SAQ	ZDV+ddC+SAQ	ddC	SAQ	SAQ+ddC
n Enrolled	17	19	20	100	99	98	314	318	308
Prior ZDV									
n	—	—	—	99	98	97	305	315	304
Median Duration (days)	—	—	—	659	713	647	521	523	477
Log_{10} Plasma RNA by PCR (copies/mL)									
n	17	19	20	100	97	96	300	307	294
Mean Baseline (n)	5.2 (17)	5.2 (19)	5.3 (20)	4.7 (100)	4.8 (97)	4.8 (96)	5.0 (300)	5.1 (307)	5.0 (294)
Mean Change from Baseline Week 16 (n)	-0.5 (15)	-0.2 (17)	-1.0 (17)	-0.3 (93)	0.0 (81)	-0.5 (86)	-0.4 (253)	-0.1 (262)	-0.6 (258)
Mean Change from Baseline Week 24 (n)	—	—	—	-0.2 (86)	0.0 (83)	-0.6 (84)	-0.3 (228)	-0.1 (244)	-0.6 (232)
Mean Change from Baseline Week 48 (n)	—	—	—	—	—	—	-0.3 (147)	-0.1 (167)	-0.6 (169)

*Saquinavir (SAQ) at 600 mg tid — Indicates not applicable

Caution should be exercised when administering INVIRASE to patients with hepatic insufficiency since patients with baseline liver function tests >5 times the upper limit of normal were not included in clinical studies. Although a causal relationship has not been established, exacerbation of chronic liver dysfunction, including portal hypertension, has been reported in patients with underlying hepatitis B or C, cirrhosis or other underlying liver abnormalities.

There have been reports of spontaneous bleeding in patients with hemophilia A and B treated with protease inhibitors. In some patients additional factor VIII was required. In the majority of reported cases treatment with protease inhibitors was continued or restarted. A causal relationship between protease inhibitor therapy and these episodes has not been established.

Fat Redistribution: Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving protease inhibitors. A causal relationship between protease inhibitor therapy and these events has not been established and the long-term consequences are currently unknown.

Resistance/Cross-resistance: The potential for HIV cross-resistance between protease inhibitors has not been fully explored. Therefore, it is unknown what effect saquinavir therapy will have on the activity of subsequent protease inhibitors (see *Microbiology*).

Information for Patients: Patients should be informed that INVIRASE is not a cure for HIV infection and that they may continue to acquire illnesses associated with advanced HIV infection, including opportunistic infections. Patients should be advised that INVIRASE should be used only in combination with an active nucleoside analogue regimen.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving protease inhibitors and that the cause and long-term health effects of these conditions are not known at this time.

Patients should be told that the long-term effects of INVIRASE are unknown at this time. They should be informed that INVIRASE therapy has not been shown to reduce the risk of transmitting HIV to others through sexual contact or blood contamination.

Patients should be advised that INVIRASE should be taken within 2 hours after a full meal (see *Pharmacokinetics*). When INVIRASE is taken without food, concentrations of saquinavir in the blood are substantially reduced and may result in no antiviral activity.

Laboratory Tests: Clinical chemistry tests should be performed prior to initiating INVIRASE therapy and at appropriate intervals thereafter. For comprehensive information concerning laboratory test alterations associated with use of individual nucleoside analogues, physicians should refer to the complete product information for these drugs.

Drug Interactions: *METABOLIC ENZYME INDUCERS:* INVIRASE should not be administered concomitantly with rifampin, since rifampin decreases saquinavir concentrations by 80% (see *Pharmacokinetics*). Rifabutin also substantially reduces saquinavir plasma concentrations by 40%. Other drugs that induce CYP3A4 (eg, phenobarbital, phenytoin, dexamethasone, carbamazepine) may also reduce saquinavir plasma concentrations. If therapy with such drugs is warranted, physicians should consider using alternatives when a patient is taking INVIRASE.

OTHER POTENTIAL INTERACTIONS: Coadministration of terfenadine, astemizole or cisapride with drugs that are known to be potent inhibitors of the cytochrome P4503A pathway (ie, ketoconazole, itraconazole, etc.) may lead to elevated plasma concentrations of terfenadine, astemizole or cisapride, which may in turn prolong QT intervals leading to rare cases of serious cardiovascular adverse events. Although INVIRASE is not a strong inhibitor of cytochrome P4503A, pharmacokinetic interaction studies with INVIRASE and terfenadine, astemizole or cisapride have not been conducted. Physicians should use alternatives to terfenadine, astemizole or cisapride when a patient is taking INVIRASE. Other compounds that are substrates of CYP3A4 (eg, calcium channel blockers, clindamycin, dapsone, quinidine, triazolam) may have elevated plasma concentrations when coadministered with INVIRASE; therefore, patients should be monitored for toxicities associated with such drugs.

ANTI-HIV COMPOUNDS: Nelfinavir: Coadministration of nelfinavir with saquinavir (given as FORTOVASE, 1200 mg) resulted in an 18% increase in nelfinavir plasma AUC and a 4-fold increase in saquinavir plasma AUC. If used in combination with saquinavir hard gelatin capsules at the recommended dose of 600 mg tid, no dose adjustments are needed. Currently, there are no safety and efficacy data available from the use of this combination.

Ritonavir: Following approximately 4 weeks of a combination regimen of saquinavir (400 or 600 mg bid) and ritonavir (400 or 600 mg bid) in HIV-positive patients, saquinavir AUC values were at least 17-fold greater than historical AUC values from patients who received saquinavir 600 mg tid without ritonavir. When used in combination therapy for up to 24 weeks, doses greater than 400 mg bid of either ritonavir or

saquinavir were associated with an increase in adverse events.

Delavirdine: Saquinavir AUC increased 5-fold when delavirdine (400 mg tid) and saquinavir (600 mg tid) were administered in combination. Currently, there are limited safety and no efficacy data available from the use of this combination. In a small, preliminary study, hepatocellular enzyme elevations occurred in 15% of subjects during the first several weeks of the delavirdine and saquinavir combination (6% Grade 3 or 4). Hepatocellular enzymes (ALT/AST) should be monitored frequently if this combination is prescribed.

Nevirapine: Coadministration of nevirapine with INVIRASE resulted in a 24% decrease in saquinavir plasma AUC. Currently, there are no safety and efficacy data available from the use of this combination.

ERECTILE DYSFUNCTION AGENTS:

Sildenafil: In a study performed in healthy male volunteers, coadministration of saquinavir, a CYP3A4 inhibitor, at steady state (1200 mg tid) with sildenafil (100 mg single dose) resulted in a 140% increase in sildenafil C_{max} and a 210% increase in sildenafil AUC. Sildenafil had no effect on saquinavir pharmacokinetics. When sildenafil is administered concomitantly with saquinavir a starting dose of 25 mg of sildenafil should be considered.

Carcinogenesis, Mutagenesis and Impairment of Fertility: *Carcinogenesis:* Carcinogenicity studies in rats and mice have not yet been completed.

Mutagenesis: Mutagenicity and genotoxicity studies, with and without metabolic activation where appropriate, have shown that saquinavir has no mutagenic activity in vitro in either bacterial (Ames test) or mammalian cells (Chinese hamster lung V79/HPRT test). Saquinavir does not induce chromosomal damage in vivo in the mouse micronucleus assay or in vitro in human peripheral blood lymphocytes, and does not induce primary DNA damage in vitro in the unscheduled DNA synthesis test.

Impairment of Fertility: Fertility and reproductive performance were not affected in rats at plasma exposures (AUC values) up to five times those achieved in humans at the recommended dose.

Pregnancy: *Teratogenic Effects:* Category B. Reproduction studies conducted with saquinavir in rats have shown no embryotoxicity or teratogenicity at plasma exposures (AUC values) up to five times those achieved in humans at the recommended dose or in rabbits at plasma exposures four times those achieved at the recommended clinical dose. Studies in rats indicated that exposure to saquinavir from late pregnancy through lactation at plasma concentrations (AUC values) up to five times those achieved in humans at the recommended dose had no effect on the survival, growth and development of offspring to weaning. Because animal reproduction studies are not always predictive of human response, INVIRASE should be used during pregnancy after taking into account the importance of the drug to the mother. Presently, there are no reports of infants being born after women receiving INVIRASE in clinical trials became pregnant.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to antiretroviral medications, including INVIRASE, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers: **The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.** It is not known whether saquinavir is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving antiretroviral medications, including INVIRASE.**

Pediatric Use: Safety and effectiveness of INVIRASE in HIV-infected pediatric patients younger than 16 years of age have not been established.

Geriatric Use: Clinical studies of INVIRASE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be taken when dosing INVIRASE in elderly patients due to the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS: (see PRECAUTIONS): The safety of INVIRASE was studied in patients who received the drug either alone or in combination with ZDV and/or HIVID (zalcitabine, ddC). The majority of adverse events were of mild intensity. The most frequently reported adverse events among patients receiving INVIRASE (excluding those toxicities known to be associated with ZDV and HIVID when used in combinations) were diarrhea, abdominal discomfort and nausea.

INVIRASE did not alter the pattern, frequency or severity of known major toxicities associated with the use of HIVID and/or ZDV. Physicians should refer to the complete product information for these drugs (or other antiretroviral agents as appropriate) for drug-associated adverse reactions to other nucleoside analogues.

In an open-label protocol, NV15114, in which 33 patients received treatment with INVIRASE, ZDV and lamivudine for 4 to 16 weeks, no unexpected toxicities were reported.

Table 4 lists clinical adverse events that occurred in ≥2% of patients receiving INVIRASE 600 mg tid alone or in combination with ZDV and/or HIVID in two trials. Median duration of treatment in NV14255/ACTG229 (triple-combination study) was 48 weeks; median duration of treatment in NV14256 (double-combination study) was approximately 1 year.

Table 4. Percentage of Patients, by Study Arm, With Clinical Adverse Experiences Considered at Least Possibly Related to Study Drug or of Unknown Relationship and of Moderate, Severe or Life-threatening Intensity, Occurring in ≥2% of Patients in NV14255/ACTG229 and NV14256

	NV14255/ACTG229			NV14256		
ADVERSE EVENT	SAQ+ZDV n=99	SAQ+ddC+ZDV n=98	ddC+ZDV n=100	ddC n=325	SAQ n=327	SAQ+ddC n=318
GASTROINTESTINAL						
Diarrhea	3.0	1.0	–	0.9	4.9	4.4
Abdominal Discomfort	2.0	3.1	4.0	0.9	0.9	0.9
Nausea	–	3.1	3.0	1.5	2.4	0.9
Dyspepsia	1.0	1.0	2.0	0.6	0.9	0.9
Abdominal Pain	2.0	1.0	2.0	0.6	1.2	0.3
Mucosa Damage	–	–	4.0	–	–	0.3
Buccal Mucosa Ulceration	–	2.0	2.0	6.2	2.1	3.8
CENTRAL AND PERIPHERAL NERVOUS SYSTEM						

Headache	2.0	2.0	2.0	3.4	2.4	0.9
Paresthesia	2.0	3.1	4.0	1.2	0.3	0.3
Extremity Numbness	2.0	1.0	4.0	1.5	0.6	0.9
Dizziness	–	2.0	1.0	–	0.3	–
Peripheral Neuropathy	–	1.0	2.0	11.4	3.1	11.3
BODY AS A WHOLE						
Asthenia	6.1	9.2	10.0	–	0.3	–
Appetite Disturbances	–	1.0	2.0	–	–	–
SKIN AND APPENDAGES						
Rash	–	–	3.0	1.5	2.1	1.3
Pruritus	–	–	2.0	–	0.6	–
MUSCULOSKELETAL DISORDERS						
Musculoskeletal Pain	2.0	2.0	4.0	0.6	0.6	0.6
Myalgia	1.0	–	3.0	0.6	0.3	0.3

- Indicates no events reported

Rare occurrences of the following serious adverse experiences have been reported during clinical trials of INVIRASE and were considered at least possibly related to use of study drugs: confusion, ataxia and weakness; acute myeloblastic leukemia; hemolytic anemia; attempted suicide; Stevens-Johnson syndrome; seizures; severe cutaneous reaction associated with increased liver function tests; isolated elevation of transaminases; thrombophlebitis; headache; thrombocytopenia; exacerbation of chronic liver disease with Grade 4 elevated liver function tests, jaundice, ascites, and right and left upper quadrant abdominal pain; drug fever; bullous skin eruption and polyarthritis; pancreatitis leading to death; nephrolithiasis; thrombocytopenia and intracranial hemorrhage leading to death; peripheral vasoconstriction; portal hypertension; intestinal obstruction. These events were reported from a database of >6000 patients. Over 100 patients on saquinavir therapy have been followed for >2 years.

Table 5 shows the percentage of patients with marked laboratory abnormalities in studies NV14255/ACTG229 and NV14256. Marked laboratory abnormalities are defined as a Grade 3 or 4 abnormality in a patient with a normal baseline value or a Grade 4 abnormality in a patient with a Grade 1 abnormality at baseline (ACTG Grading System).

Table 5. Percentage of Patients, by Treatment Group, With Marked Laboratory Abnormalities* in NV14255/ACTG229 and NV14256

	NV14255/ACTG229			NV14256		
	SAQ+ZDV n=99	SAQ+ddC+ZDV n=98	ddC+ZDV n=100	ddC n=325	SAQ n=327	SAQ+ddC n=318
BIOCHEMISTRY						
Calcium (high)	1	0	0	<1	0	0
Calcium (low)	—	—	—	<1	<1	0
Creatine Phosphokinase (high)	10	12	7	6	3	7
Glucose (high)	0	0	0	<1	1	1
Glucose (low)	0	0	0	5	5	5
Phosphate (low)	2	1	0	0	<1	<1
Potassium (high)	0	0	0	2	2	3
Potassium (low)	0	0	0	0	1	0
Serum Amylase (high)	2	1	1	2	1	1
SGOT (AST) (high)	2	2	0	2	2	3
SGPT (ALT) (high)	0	3	1	2	2	2
Sodium (high)	—	—	—	0	0	<1
Sodium (low)	—	—	—	0	<1	0
Total Bilirubin (high)	1	0	0	0	<1	1
Uric Acid	0	0	1	Not assessed	Not assessed	Not assessed
HEMATOLOGY						
Neutrophils (low)	2	2	8	1	1	1
Hemoglobin (low)	0	0	1	<1	<1	0
Platelets (low)	0	0	2	1	1	<1

* Marked Laboratory Abnormality defined as a shift from Grade 0 to at least Grade 3 or from Grade 1 to Grade 4 (ACTG Grading System)

Monotherapy and Combination Studies: Other clinical adverse experiences of any intensity, at least remotely related to INVIRASE, including those in <2% of patients on arms containing INVIRASE in studies NV14255/ACTG229 and NV14256, and those in smaller clinical trials, are listed below by body system.

Body as a Whole: Allergic reaction, anorexia, chest pain, edema, fatigue, fever, intoxication, parasites external, retrosternal pain, shivering, wasting syndrome, weakness generalized, weight decrease, redistribution/accumulation of body fat (see PRECAUTIONS: *Fat Redistribution*)

Cardiovascular: Cyanosis, heart murmur, heart valve disorder, hypertension, hypotension, syncope, vein distended

Endocrine/Metabolic: Dehydration, diabetes mellitus, dry eye syndrome, hyperglycemia, weight increase, xerophthalmia

Gastrointestinal: Cheilitis, colic abdominal, constipation, dyspepsia, dysphagia, esophagitis, eructation, feces bloodstained, feces discolored, flatulence, gastralgia, gastritis, gastrointestinal inflammation, gingivitis, glossitis, hemorrhage rectum, hemorrhoids, hepatitis, hepatomegaly, hepatosplenomegaly, infectious diarrhea, jaundice, liver enzyme disorder, melena, pain pelvic, painful defecation, pancreatitis, parotid disorder, salivary glands disorder, stomach upset, stomatitis, toothache, tooth disorder, vomiting

Hematologic: Anemia, bleeding dermal, microhemorrhages, neutropenia, pancytopenia, splenomegaly, thrombocytopenia

Musculoskeletal: Arthralgia, arthritis, back pain, cramps leg, cramps muscle, creatine phosphokinase increased, musculoskeletal disorders, stiffness, tissue changes, trauma

Neurological: Ataxia, bowel movements frequent, confusion, convulsions, dysarthria, dysesthesia, heart rate disorder, hyperesthesia, hyperreflexia, hyporeflexia, light-headed feeling, mouth dry, myelopolyradiculoneuritis, numbness face, pain facial, paresis, poliomyelitis, prickly sensation, progressive multifocal leukoencephalopathy, spasms, tremor, unconsciousness

Psychological: Agitation, amnesia, anxiety, anxiety attack, depression, dreaming excessive, euphoria, hallucination, insomnia, intellectual ability reduced, irritability, lethargy, libido disorder, overdose effect, psychic disorder, psychosis, somnolence, speech disorder, suicide attempt

Reproductive System: Impotence, prostate enlarged, vaginal discharge

Resistance Mechanism: Abscess, angina tonsillaris, candidiasis, cellulitis, herpes simplex, herpes zoster, infection bacterial, infection mycotic, infection staphylococcal, influenza, lymphadenopathy, moniliasis, tumor

Respiratory: Bronchitis, cough, dyspnea, epistaxis, hemoptysis, laryngitis, pharyngitis, pneumonia, pulmonary disease, respiratory disorder, rhinitis, sinusitis, upper respiratory tract infection

Skin and Appendages: Acne, alopecia, chalazion, dermatitis, dermatitis seborrheic, eczema, erythema, folliculitis, furunculosis, hair changes, hot flushes, nail disorder, night sweats, papillomatosis, photosensitivity reaction, pigment changes skin, rash maculopapular, skin disorder, skin nodule, skin ulceration, sweating increased, urticaria, verruca, xeroderma

Special Senses: Blepharitis, earache, ear pressure, eye irritation, hearing decreased, otitis, taste alteration, tinnitus, visual disturbance

Urinary System: Micturition disorder, renal calculus, urinary tract bleeding, urinary tract infection

OVERDOSAGE: No acute toxicities or sequelae were noted in 1 patient who ingested 8 grams of INVIRASE as a single dose. The patient was treated with induction of emesis within 2 to 4 hours after ingestion. In an exploratory Phase 2 study of oral dosing with INVIRASE at 7200 mg/day (1200 mg q4h), there were no serious toxicities reported through the first 25 weeks of treatment.

DOSAGE AND ADMINISTRATION: INVIRASE (saquinavir mesylate) capsules and FORTOVASE (saquinavir) soft gelatin capsules are not bioequivalent and cannot be used interchangeably. When using saquinavir as part of an antiviral regimen FORTOVASE is the recommended formulation. In rare circumstances, INVIRASE may be considered if it is to be combined with antiretrovirals that significantly inhibit saquinavir's metabolism (see CLINICAL PHARMACOLOGY: *DRUG INTERACTIONS*).

The recommended dose for INVIRASE in combination with a nucleoside analogue is three 200-mg capsules three times daily taken within 2 hours after a full meal. Please refer to the complete product information for each of the nucleoside analogues for the recommended doses of these agents.

INVIRASE should be used only in combination with an active antiretroviral nucleoside analogue regimen. Concomitant therapy should be based on a patient’s prior drug exposure.

Monitoring of Patients: Clinical chemistry tests should be performed prior to initiating INVIRASE therapy and at appropriate intervals thereafter. For comprehensive patient monitoring recommendations for other nucleoside analogues, physicians should refer to the complete product information for these drugs.

Dose Adjustment for Combination Therapy With INVIRASE: For toxicities that may be associated with INVIRASE, the drug should be interrupted. INVIRASE at doses less than 600 mg tid are not recommended since lower doses have not shown antiviral activity. For recipients of combination therapy with INVIRASE and nucleoside analogues, dose adjustment of the nucleoside analogue should be based on the known toxicity profile of the individual drug. Physicians should refer to the complete product information for these drugs for comprehensive dose adjustment recommendations and drug-associated adverse reactions of nucleoside analogues.

HOW SUPPLIED: INVIRASE 200-mg capsules are light brown and green opaque capsules with ROCHE and 0245 imprinted on the capsule shell — bottles of 270 (NDC 0004-0245-15).

The capsules should be stored at 59° to 86°F (15° to 30°C) in tightly closed bottles.

R_x only

Manufactured by:
F. Hoffmann-La Roche Ltd., Basel, Switzerland or
Hoffmann-La Roche Inc., Nutley, New Jersey
Distributed by:

Roche Pharmaceuticals

Roche Laboratories Inc., 340 Kingsland Street, Nutley, New Jersey 07110-1199

27897176-09000

Revised: September 2000
Printed in USA